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Report on

Medical Equipment and Pharmaceuticals Market-Oriented, Sector-Selective (MOSS) Discussions

by the

U.S. and Japan MOSS Negotiating Teams

to

Minister for Foreign Affairs Abe
Secretary of State Shultz

January 1986

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January 1986

January 9, 1986

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Ministry of Foreign Affairs
Tokyo

Secretary of State George P. Shultz
Department of State
Washington, D.C.

We are pleased to forward to you the attached official copy of the report by our negotiating teams on the market-oriented, sector-selective (MOSS) talks on medical equipment and pharmaceuticals. We believe that this report is responsive to the mandate entrusted to us.

Respectfully,

吉村 仁

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Ministry of Health
and Welfare
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David C. Mulford
Assistant Secretary for
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MEDICAL EQUIPMENT AND PHARMACEUTICALS MARKET-ORIENTED,
SECTOR-SELECTIVE (MOSS) DISCUSSIONS

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I. INTRODUCTION

A. OVERVIEW OF THE DISCUSSIONS

On January 2, 1985, President Reagan and Prime Minister Nakasone met in Los Angeles to discuss, among other issues, bilateral economic issues. The MOSS talks resulted from that meeting.

On January 28 and 29, 1985, high-level officials from Japan and the United States met in Tokyo to launch the process agreed to by the President and the Prime Minister. The United States presented an approach that was market-oriented and sector-selective, with the acronym MOSS. The market-oriented aspect of this approach meant focusing on removing barriers that limit market access. The sector-selective aspect meant undertaking this barrier-removal within specific industrial sectors -- telecommunications, medical equipment and pharmaceuticals, electronics, and forest products -- discussed by the President and the Prime Minister. The Japanese side indicated that it was willing to follow this MOSS approach.

The MOSS discussions in the medical equipment and pharmaceuticals sector between the governments of the United States and Japan concentrated on further opening the Japanese health care market by addressing the trade effects of Japan's regulatory system for protecting public health and safety and its insurance system for reimbursing health care expenses. The MOSS discussions covered the full spectrum of product marketing, including manufacturing or import approvals (shonin), licensing for manufacture or import (kyoka), and pricing.

The U.S. side raised the market-opening issues from the viewpoint of removing barriers to trade and/or to the conduct of business in Japan by foreign firms. The U.S. side stated that in many cases the issues reflected inefficiencies and inflexibilities in the regulatory system which had the effect of impeding the entrance into the market of new producers and new products, and of influencing business decisions even when health and safety questions were not at stake. At the same time, the U.S. side did not question the basic mandate of the Ministry of Health and Welfare (MHW) under the Pharmaceutical Affairs Law (PAL) to regulate in favor of the health and safety of the Japanese people and the overall objective of MHW to reduce Japanese health care expenses.

The Japanese side responded that the Japanese regulatory system neither overtly nor covertly discriminated against foreign firms in favor of domestic ones, providing both with equal opportunities to enter the health care market. It recognized, however, the importance of simplifying administrative procedures, eliminating administrative delays, and increasing transparency, for further facilitating access to Japan's market and strengthening the free trade system. The Japanese side agreed to discuss and seek solutions to the issues as presented in this way.

The interagency delegations of both sides met six times in 1985 to discuss and develop market-opening measures, and worked intensively to realize the intent of the MOSS initiative. As a result, important progress has been made through these discussions and improvements in access to Japan's market have been and will be realized.

This report describes the problems addressed in the talks and the particular issues of market access which they involved. It explains the solutions to the issues to which both sides agreed. It specifies future work plans of both sides in this sector.

The measures agreed to by the United States and Japan should eliminate the adverse trade effects of the regulatory system while continuing to safeguard the health and safety of the Japanese people. To further these objectives, both sides have agreed to continue to meet on a regular basis to review implementation of the agreed solutions and to resolve any complications that may arise.

The U.S. side was led by Assistant Secretary of the Treasury for International Affairs David C. Mulford. The Japanese side was led by Vice Minister of MHW Hitoshi Yoshimura.

B. SUMMARY OF THE AGREED SOLUTIONS

Chapter II of this report provides more detailed descriptions of the issues and the agreements that resolved them. This section is a summary, described in the context of the relevant operational features of the Japanese health care regulatory system, of the specific measures or commitments agreed upon by the MOSS negotiators.

1. Main Features of the Japanese Health Care Regulatory System

The elements of the regulatory system most relevant to the discussions and on which the negotiators concentrated involved the processes for obtaining relevant approvals and licenses and the listing of reimbursement prices under the comprehensive Japanese medical insurance system. To bring a product to market, the initial step for foreign and domestic producers alike is to obtain manufacturing or import approvals of the pharmaceutical or medical device products themselves. Such approvals are called shonin, and obtaining them depends essentially upon documentation, including the results of clinical testing, which can satisfy MHW that safety and efficacy requirements are met. In its decision-making process, MHW consults with an advisory body, the Central Pharmaceutical Affairs Council (CPAC), which investigates from a scientific point of view whether it is appropriate to approve manufacturing or import of new pharmaceutical or medical device products.

To produce or import a drug or medical device, a license to manufacture or import, called a kyoka, must also be obtained on the basis of documentation which demonstrates (1) that producing or importing establishments meet appropriate safety and manufacturing standards, and (2) that board members of the manufacturer or importer are legally able to serve in that capacity.

The shonin is granted to each person (or juridical person) intending to manufacture or import drugs or devices. The kyoka is granted for each manufacturing plant or importer's business office.

With shonin and kyoka in hand, a firm is technically qualified to bring a product to market. Nevertheless, sales of the product, in general, depend heavily upon reimbursement under the National Health Insurance scheme, because it covers practically 100 percent of the Japanese population. Therefore, the manufacturer or importer must seek an appropriate price listing under the system. The insurance price listing process is separate from the approvals processes which generate shonin and kyoka. Prices are set by MHW based on general rules formulated by the Social Insurance Medical Affairs Council (Chuikyo), which is the organ for reconciliation of the interests of payers and payees of insurance reimbursement.

2. The Issues and Their Resolutions

The specific issues discussed by the negotiators can be grouped under the following headings, each of which corresponds to an aspect of the approval and reimbursement price-setting processes: (a) testing and test data; (b) approval and licensing processes themselves; (c) linkages between the approval and pricing mechanisms; (d) the National Health Insurance reimbursement system; and (e) transparency. Generally, the negotiators sought solutions which would protect the integrity of MHW's mandate under the PAL to protect the health and safety of the Japanese people; eliminate delays in marketing new products; eliminate sources of unnecessarily higher costs of doing business in Japan; and improve the commercial business decision-making environment in Japan.

a. Testing and Test Data

Regulatory authorities in both Japan and the United States require firms to submit detailed reports on pre-clinical and clinical drug and device trials in support of approval applications. At the negotiations, the U.S. delegation pointed out that Japanese clinical testing requirements in effect for the shonin caused problems for foreign firms in terms of costly delays in approvals and higher costs of doing business. The U.S. side noted that MHW required all clinical testing to be done in Japan on resident Japanese citizens. This required costly duplication of testing performed elsewhere in the world, even when differences among test subjects may not have had any bearing on the results. It introduced delays which could prevent new products from entering the Japanese market quickly. Domestic firms did not bear these duplicative testing costs. Problems of duplicative testing requirements raised by the U.S. side extended to pharmaceuticals, medical devices, and in-vitro diagnostics.

The Japanese side noted that it was aware of problems in the testing field. Prior to the MOSS talks, it had established a group of scientific experts to study the issue of acceptance of foreign clinical test data.

The negotiators also noted certain other testing issues which concerned Japan's inspection requirements for blood and other biologicals, as well as stability and sterility testing standards.

The negotiators reached the following agreements on the testing and test data issues:

(1) Acceptance of Foreign Clinical Data

-- With regard to pharmaceuticals, foreign clinical test data will now be accepted for all examination and testing

requirements except for the following three items where there are immunological and ethnic differences between Japanese and foreigners:

- o Comparative clinical trials;
- o Dose finding tests; and
- o Absorption, distribution, metabolism, and excretion tests.

-- For in-vitro diagnostic reagents, foreign clinical test data will now be accepted except for those with new parameters (i.e., those which measure an entirely new substance as a diagnostic indicator), and those in which immunological reaction problems could occur with the materials to be tested.

-- Foreign clinical test data will now be accepted for medical devices, except implantables and those affecting organic adaptability.

(2) Other Testing Issues

-- In a series of experts' meetings, both sides agreed on significant improvements in Japan's testing requirements for stability and sterility tests and for blood and other biological products.

b. Approval and Licensing Processes

The MOSS talks explored numerous business issues raised by the U.S. side as affecting foreign firms in working through the processes of obtaining shonin and kyoka, and in amending these documents as business requirements and relationships changed.

-- MHW had no standard processing periods for new approvals. This often caused costly uncertainties and delays and it may have created perceptions in the eyes of foreign firms of arbitrariness in the system.

-- No distinctive system existed for pre-market review of in-vitro diagnostic reagents. As a result, firms encountered costly delays in bringing products to market, and innovative products could not reach the market quickly.

-- The regulatory system did not provide for "transfers" of shonin from one business entity to another. This difficult issue dealt with a core principle of the regulatory system which the Japanese side believed could not and should not be changed, but at the same time, the U.S. delegation noted, it inhibited the full exercise of proprietary rights to products.

-- The system could not deal simply or easily with unique combinations of drugs and devices (e.g., the combination into a single package of a drug and its delivery system). Such packages are increasingly used in world markets. They are technologically advanced, medically superior, and able to offer great cost savings in medical care.

-- Costly documentation requirements and regulatory impediments were placed on foreign firms wishing to:

  o Change the country of manufacture of already approved products;

  o Make minor modifications and improvements to already approved products; or

  o Change the addresses of importers in Japan without disrupting business operations.

-- Importers of drugs and devices encountered administrative delays in import procedures because Customs and MHW import clearance operations were not integrated. This problem increased importers' costs and impeded efficient trade.

The negotiators reached mutually acceptable solutions to each of these approval process issues, as follows:

-- Standard processing periods have been adopted and published for approvals for pharmaceuticals, diagnostics, and devices. If MHW cannot process an application within the relevant standard processing period, the applicant will now have the right to be so informed and given an explanation of the reasons therefor.

-- In-vitro diagnostic reagents now have their own distinctive, expeditious approval review process. Such reagents are examined separately from other pharmaceuticals on the basis of simplified application documents.

-- For transfers of approvals: when a company wishes to change commercial arrangements (for example, from importing to licensing, from one licensee to another, or from licensing to manufacturing), and the company's former business partner agrees to transfer manufacturing or importing operations and all necessary data and information to the new partner or entity, the shonin will be transfered by notification accompanied by the evidence of their agreement. Kyoka will be issued and existing prices will be listed within three months after the date of application (prior application for kyoka will be possible). When there is no such agreement between transferor and transferee, MHW will issue shonin and

kyoka within three months of application under simplified procedures, if the applicant submits data and information similar to that for agreed transfers, and when the former business partner ceases to manufacture or import the product. The reimbursement price will be set at the same level as for the previously approved product within three months after the new shonin is issued. The U.S. and Japan have agreed to consider resolution of all types of transfer situations on a case-by-case basis as they arise within the framework of the follow-up process described in Chapter IV of the report. Both sides are committed to finding practical solutions to legitimate business problems that arise in this area.

-- MHW has devised adequate approval and pricing procedures for "kits" which combine drugs and their delivery systems. Such kits can now be brought to the Japanese market and priced appropriately under the insurance reimbursement system.

-- Firms exporting approved drugs or medical devices to Japan that wish to change their country of manufacture need only notify MHW; approval modifications are no longer required.

-- MHW has clarified by official notice the scope and types of minor product modifications which do not require approvals.

-- Importers wishing to change locations of facilities or places of business may now make advance application for kyoka, based on newly simplified documentation, so that business operations are not disrupted.

-- The customs clearance process for imported products has been streamlined to provide for "one stop" service. If importers have MHW approvals and licenses under the PAL, their goods can be cleared by Customs officials under normal customs procedures.

c. Linkages Between Approval and Pricing Mechanisms

Because the regulatory machinery governing approvals was separated from the pricing machinery of the National Health Insurance system, a key issue for the negotiators was the elimination of delays between the granting of shonin and the setting of reimbursement prices. Such delays added to the costs and uncertainties faced by firms doing business in Japan.

The negotiators agreed on significant increases in the frequency of pricing decisions for drugs and medical devices (see discussion on timing of reimbursement prices, below). These changes will serve to link approval decisions much more closely with pricing decisions,

thus significantly reducing the delays and uncertainties that add to the costs of firms.

d. The National Health Insurance Reimbursement System

Several major issues resolved by the negotiators applied to the reimbursement pricing system itself. In the discussions the U.S. side did not question the overall objective of MHW to reduce Japanese health care costs. It did seek, however, a pricing system which would operate more regularly and speedily, under clearly defined criteria.

-- At the outset of the negotiations, the U.S. side asserted that the listing of reimbursement rates was too irregular and generally infrequent. This situation produced for firms not only uncertainty but costly delays in market entry even after the hurdles of obtaining shonin and kyoka had been surmounted.

-- The U.S. team also observed that criteria set by the Chuikyo in its deliberations and used by MHW in deciding how to set reimbursement prices as well as what prices to set were unclear. This hindered the ability of firms to communicate efficiently the precise information needed to speed pricing decisions and make them responsive to costs of doing business.

The negotiators agreed that for all new drugs and many medical devices (including many in-vitro diagnostics), price listings will be provided quarterly -- a significant increase in frequency that will reduce delays between approval and price listing to no more than 90 days; in addition, MHW has committed itself in principle to delays of no more than 60 days (in limited cases, such as when few items are ready for listing and pricing issues are not controversial, it might be possible to shorten the delay to about 30 days). New, innovative in-vitro diagnostics (those in Class I, in the MHW classification) will be introduced into the reimbursement system within six months after their approvals. These changes will be implemented during Japan's fiscal year (JFY) 1986.

As regards the criteria set by the Chuikyo in its deliberations and used by MHW, several changes were agreed upon by the negotiators. The formulas used for calculating new drug prices and for revising drug tariff standards will be made public. When these formulas are to be changed, opportunities will be provided for foreign as well as domestic industry representatives to express their views on general issues of reimbursement policy. In addition, MHW, after consultation with the Chuikyo, will establish and announce in JFY 1986 its general rules for setting and revising prices of medical devices and in-vitro diagnostics.

e. Transparency

When the MOSS talks began, the U.S. team noted that foreign firms had insufficient opportunity to communicate with the regulatory authorities on technical matters in order to speed up and improve the regulatory processes for medical products. A pledge to increase transparency in all regulatory bodies is a key element of Japan's market-opening efforts, as stated clearly by Prime Minister Nakasone in July 1985. The U.S. side requested that transparency principles be extended to all aspects of the Japanese regulatory process, including the Central Pharmaceutical Affairs Council (CPAC), the Chuikyo, and MHW itself.

During the course of the talks, the U.S. delegation noted with appreciation that MHW had steadily increased both the frequency and the openness of formal and informal discussion on approvals and other matters with foreign firms and their representative groups. U.S. contact with representatives of foreign firms revealed a high level of satisfaction on the part of those businesses with this progressive attitude of MHW officials at all levels. MHW confirmed that it will continue this successful policy.

The negotiators agreed on several formal steps to increase the transparency of the regulatory system. The CPAC's "Common Instructions" will be made public and meetings will be held to explain them. During CPAC deliberations, applicants for new drug approvals will receive opportunities to hear instructions from CPAC members, to ask questions, and to comment on the Council's instructions. As noted above, foreign as well as domestic industry representatives will be able to present their views to the Chuikyo on general reimbursement policy issues when the general rules of the tariff for medical fees or the drug tariff are to be established or changed. After consultation with the Chuikyo, MHW also will establish during JFY 1986 procedures for closed hearings at which individual company representatives (including product originators if they wish to accompany applicant firm representatives) may state to MHW their opinions on pricing of their particular products; these hearings will receive testimony on efficacy, desired prices, and other arguments regarding the product prices at issue; and MHW will provide adequate prior public notice when the hearings are to be held.

II. ISSUES RESOLVED

A. ACCEPTANCE OF FOREIGN CLINICAL TEST DATA

1. Issue

In both the United States and Japan, manufacturers of medical devices and pharmaceuticals must submit new products to extensive batteries of pre-clinical and clinical trials in order to demonstrate adequate safety and efficacy. The data derived from these trials provide the instrumental basis for regulatory decisions.

Japan's regulatory authorities historically had not accepted foreign-generated clinical test data. In other words, irrespective of a product's testing history abroad, a foreign firm had to perform all of the clinical trials required by the Japanese approval process, on Japanese subjects in Japan.

The U.S. side explained that these testing requirements had two serious market effects. First, the duplication of testing, which is extremely costly, placed upon foreign firms a cost burden which their domestic competitors in Japan did not have to face. Second, duplicative testing in Japan brought about delays in product marketing.

The Japanese side noted that it was aware of problems in this regard, and that it had established a group of scientific experts to study the problem of the acceptance of foreign clinical data.

2. Agreed Approach

Experts-level discussions took place between the U.S. Food and Drug Administration (FDA) and MHW in May 1985 in Rockville, Maryland, regarding each nation's policies for the acceptance of foreign clinical test data in making regulatory approvals. At that time experts discussed the possibility of setting, bilaterally or multilaterally, common standards for the acceptance of foreign clinical test data. The FDA and MHW agreed in principle that it is desirable to work toward a system of international harmonization. Following these expert discussions, the United States and Japan resolved at their June 1985 talks in Tokyo to promote the acceptance of foreign clinical test data for regulatory purposes in Japan.

Japan agreed to accept foreign clinical test data for regulatory approval of pharmaceuticals, medical devices, and in-vitro diagnostic reagents, as follows:

(1) With regard to pharmaceuticals, foreign clinical test data will now be accepted for all examination/testing

requirements except for the following three items where there are immunological and ethnic differences between Japanese and foreigners: comparative clinical trials; dose finding tests; and absorption, distribution, metabolism, and excretion tests.

(2) Foreign clinical test data will now be accepted for in-vitro diagnostic reagents except those with new parameters (i.e., those which measure an entirely new substance as a diagnostic indicator), and those in which immunological reaction problems could occur with the materials to be tested.

(3) Foreign clinical test data will now be accepted for medical devices except those implanted in the human body and those affecting organic adaptability.

The relevant regulatory action taken by Japan is as follows:

-- Notification No. 660, "Handling of Foreign Clinical Data for Pharmaceuticals, etc." (dated: June 29, 1985; effective: July 31, 1985).

B. "TIME CLOCK" OR "STANDARD PROCESSING PERIOD" FOR NEW APPROVALS

1. Issue

The U.S. side sought the adoption in Japan of a system of standard processing periods analogous to that used in the United States. The U.S. side said that standard processing periods would remove the possibility for excessive delays in licensing which sometimes occurred in the Japanese system, and generally eliminate costly uncertainties which affected both Japanese and foreign firms. It would contribute to and hasten progress toward the ultimate goal of shortening the approval processes.

2. Agreed Approach

As of October 1, 1985, MHW introduced standard processing periods analogous to the FDA's "time clock" procedures. These standard periods are understood as outer limits for the approval process; where feasible, as in the past, application processing times can and will be shorter. If an application cannot be processed within these periods, the applicant will be so informed and given the reason. MHW can "stop the clock" only when it is necessary for the applicant to correct incomplete applications, conduct additional tests, or answer inquiries from MHW. The standard processing periods begin with the submission of applications to prefectural offices and end with the issuance of shonin in Tokyo. (Note: The kyoka is normally issued simultaneously with the shonin.) The approval takes effect when issued by MHW in Tokyo.

The standard processing periods are as follows:

New Drugs:	Eighteen Months
"Me-Too" Drugs:	Two Years*
OTC Drugs:	Ten Months
In-Vitros:	Six Months
Quasi-Drugs:	Six Months
Medical Devices:	One Year
"Me-Too" Devices:	Four Months
Cosmetics:	Three Months

The relevant regulatory action taken by Japan is as follows:

-- Notification No. 960, "Setting of Standard Processing Periods" (dated: October 1, 1985; effective: October 1, 1985).

*Provisional.

C. REGULATION OF IN-VITRO DIAGNOSTIC REAGENTS

1. Issue

The field of in-vitro diagnostic reagents is a rapidly changing, highly innovative, and complex market. Product cycles can be very short as product advances are made. Prior to the MOSS negotiations, Japan had no distinctive system for premarket review to speed the issuance of shonin for these products. As a result, foreign firms, the U.S. side explained, sometimes faced delay and uncertainty which can preclude market entry when product cycles are short and constant change in technology is pervasive.

The discussions centered on streamlining the Japanese approach to regulation in this area so that the system could (1) respond quickly and efficiently to major or minor modifications in already approved products, and (2) reserve for stronger regulatory scrutiny only those cases where safety and efficacy considerations require it.

2. Agreed Approach

When experts of FDA and MHW met in May 1985 in Rockville, Maryland, they discussed each nation's policies for the regulation of in-vitro diagnostic products as well as for the acceptance of foreign clinical test data. Following these expert discussions, Japan announced at the June 1985 talks the promulgation of a separate regulatory channel for the approval of in-vitro diagnostic products, and also the acceptance of foreign clinical test data in approval applications as described previously. It was agreed that:

(1) Applications for in-vitro diagnostic approval will be received and examined separately from ordinary pharmaceuticals; and

(2) Three categories of in-vitro diagnostic products will be set up: (a) new parameter; (b) new method; and (c) old parameter. The approval requirements for categories (b) and (c) will be simplified.

The relevant regulatory actions taken by Japan are as follows:

-- Notification No. 662, "Handling of In-Vitro Diagnostic Reagents" (dated: June 29, 1985; effective: July 31, 1985).

-- Notification No. 5, "Handling of Shonin Application for In-Vitro Diagnostic Reagents" (dated: July 15, 1985; effective: July 31, 1985).

D. TRANSFER OF APPROVAL

1. Issue

In dynamic, rapidly changing industries, such as those making medical equipment and pharmaceuticals, economic efficiency and good business practice often require changes in commercial relationships by manufacturers and/or importers. This factor has special significance in the Japanese market for drugs and devices because, historically, foreign firms have entered the market in stages involving variously (1) importation and marketing through wholesalers, (2) importation and direct marketing, (3) licensing of manufacture to Japanese firms, and (4) establishment of subsidiaries in Japan to manufacture products that may be marketed either directly or through wholesalers. As foreign firms pass through these stages and adapt their operations to the Japanese market, changes in commercial relationships need to be smoothly accommodated, subject to legal proprietary rights (e.g., patent rights) and contracts, as well as MHW's regulatory obligations for the health and safety of the Japanese people.

The U.S. and Japanese delegations discussed Japanese procedures for smoothly allowing the transfer of approvals (shonin) to permit changes in commercial relationships in Japan. The U.S. side stated that the regulatory system restricted the ability of most foreign firms to make such changes. In order to change the manufacturer of an approved product from one entity to another, MHW required the latter to submit data and information and to obtain a new shonin. When the former was unwilling to cooperate, the change was extremely difficult.

The U.S. side stated that such difficulties in changing approvals could occur even in cases where commercial relationships, such as licensing agreements, had been legally terminated. In the U.S. view there appeared, therefore, to be a contradiction between the contractual relationship governing two business firms and the implied relationship governed by the regulatory approvals themselves, with the latter conferring and protecting market rights not contemplated by the former.

The U.S. side stated that this issue had several specific, practical implications for foreign firms attempting to do business in Japan as follows:

-- Until 1975, investment restrictions under the Foreign Exchange Control Law, which was changed in that year, generally restricted foreign firms from making direct investments in Japanese production facilities. Thus, the principal means of entry to the Japanese market that was available was to license production to Japanese firms. The U.S. side stated that firms which invested in plants in Japan after 1975 were able, but

found it extremely difficult and time-consuming, to obtain manufacturing approval because under the basic framework of the PAL the manufacturing approval has no relationship with patents and similar proprietary rights held by firms.

-- In 1983, through a revision of the PAL, Japan agreed to allow manufacturers in foreign countries to hold shonin in their own names when importers in Japan imported their products under valid kyoka. The U.S. side stated that foreign firms which previously had either licensed production in Japan or marketed in Japan through Japanese firms holding the shonin could not effectively take advantage of this 1983 change for previously approved products. The U.S. side also stated that the 1983 change thus applied only to new products imported and introduced to the Japanese market by foreign firms for the first time.

-- More generally, the U.S. side noted that MHW had no machinery for the transfer (or revocation and re-issuance to new applicants) of shonin in any of the many situations in which changing business and commercial relationships would make such transfers advantageous for foreign firms when they held clear and legally demonstrable proprietary rights (e.g., patents) under Japanese business law.

This broad issue was a difficult one for both sides. The U.S. team saw it primarily as one dealing with intellectual property, namely, the right of foreign firms to hold and benefit from their proprietary innovations as they choose, subject only to MHW's undisputed mandate to protect the health and safety of the Japanese people.

The Japanese side asserted that it is most appropriate to require the manufacturer or importer, who is within the Japanese jurisdiction, to bear all the responsibilities for efficacy, safety, and quality of the product in order to protect the health and safety of the Japanese people. For that purpose, the regulatory system requires the manufacturer or importer to obtain shonin and kyoka individually for each product. In other words, under the PAL, MHW has the grave responsibility to confirm that the manufacturer or importer has full knowledge and information on efficacy, safety, and quality control of the product and is able to do its business under all obligations imposed by the law. In that sense, the Japanese side noted, the present legislative framework is most efficient, reasonable, and practical in order to protect health and safety of the general public.

Furthermore, the Japanese side commented that the PAL, a public law for health regulation, has no concern with private

business relationships or proprietary rights governed by private laws and leaves private disputes for the Patent Law, the Civil Law, etc. Therefore, the shonin does not interfere with patents or proprietary rights.

On the other hand, the Japanese side agreed to consider simplification of relevant documents and speed-up of approval procedures for changing manufacturers to the extent that they are considered to be able to take their own responsibilities for public health and safety.

2. Agreed Approach

a. Transfers When Both Parties Agree

The transfer of manufacturing approvals will now be enabled so that firms can register in their own names all rights and titles to their products without having to regenerate and resubmit data upon the termination of the relevant business relationship with the former approval or license holder. It was agreed that the transfer of manufacturing approvals is permitted:

(1) Upon submission of a transfer notification with accompanying documentation that shows that both parties have agreed to the transfer; and

(2) Provided that the transferee receives from the transferor all data on the efficacy, safety, and quality of the relevant pharmaceutical or medical device.

After the transfer, the product's reimbursement price will be listed at the same level as that applied before the transfer. Issuance of kyoka and price listing will occur at the time of a shonin transfer if an application for kyoka and notification are received at least three months prior to the date of transfer. Otherwise, the kyoka will be issued and the price will be listed within three months after the date of application.

The relevant regulatory action taken by Japan is as follows:

-- Ministerial Ordinance No. 26 (dated: June 29, 1985; effective: July 31, 1985).

-- Notification No. 658, "Implementation of the Ministerial Ordinance for Partial Revision of the Enforcement Regulations, Pharmaceutical Affairs Law" (dated: June 29, 1985; effective: July 31, 1985); No. 1 (1) "Items Concerning Transfer of Approvals."

b. Transfers When Both Parties Do Not Agree

In the case that both parties do not agree to the transfer of manufacturing or import approval, if the applicant submits data

and information for the approval similar to that required in the case of transfers when both parties agree, and at the same time the original approval holder ceases to manufacture or import the product after the new approval is granted for the applicant, simplification of application documents, and acceleration of the approval process, will occur, with the same effect and within the same time periods as in case 2a above. The reimbursement price will be set at the same level as for the previously approved product within three months after the new shonin is issued.

c. Transfers of Manufacturing to Importing and Vice Versa

In case of changing manufacturing to importing and vice versa, application requirements and simplified procedures identical to those in case 2b above will apply. As a result, the same effect as in case 2a above will be achieved.

Official notices implementing the procedures described in paragraphs 2b and 2c above will be issued in March 1986, to take effect on April 1, 1986.

d. Follow-up

The United States and Japan have agreed to consider resolution of all types of transfer situations on a case-by-case basis as they arise within the framework of the follow-up process described in Chapter IV of the report. Both sides are committed to finding practical solutions to legitimate business problems that arise in this area.

E. APPROVAL AND REIMBURSEMENT FOR KITS

1. Issue

Among the many advances of modern medicine and health care delivery has been the emergence on the world market of procedure "kits" which combine medicines with their delivery systems in single packages. Such kits generally offer primary advantages such as shown below over predecessor (non-kit) delivery systems:

(1) They mitigate infection risks;

(2) They reduce the risk of mistakes in dosage preparation because dosages are precisely pre-packaged;

(3) They permit faster emergency treatment;

(4) They guarantee improved treatment quality;

(5) When used in clinics and hospitals, they eliminate waste and facilitate inventory control, which leads to materials cost reduction; and

(6) They are convenient, safe, and labor-saving.

During the MOSS discussions, the U.S. and Japanese delegations ascertained that Japan did not have fully consolidated application, approval, and pricing procedures for the kits, because of their distinctive features as the unique combination of drugs and delivery systems. As a result, the introduction of those new technology products into the Japanese market had been delayed. Yet such procedures needed to be worked out in order for the kits to be able to enter the Japanese market smoothly.

The U.S. side noted that the following specific difficulties needed to be solved.

Concerning approvals,

(1) MHW had no time limit within which to decide whether to approve a kit.

(2) It required manufacturers to go through the entire drug approval process for a kit even when the drug portion of the kit had already been granted approval for importation or manufacture. (On the Japanese view on drug approval, see Section D, page 15.)

(3) The sale of a kit of dual manufacture, which is becoming increasingly common as technology advances, was ruled out.

Concerning pricing,

(1) The health insurance reimbursement system covered only the drug portion of a kit and had no mechanism for reimbursing the total value of the kit so that its seller could be adequately compensated.

(2) A means had to be found for basing reimbursement prices on the truly innovative feature of a kit, namely, the unique combination of drug and delivery system which gives the kit its medical and economic advantages.

2. Agreed Approach

a. Approvals

The Government of Japan gave the U.S. Government a proposal on the approval procedures for kits. According to that proposal, MHW will accept applications for approvals for procedure kits and set reimbursement prices for kits. Either the maker of the drug component of the kit or the maker of the device component of the kit may be the holder of the approvals and may be the manufacturer of the complete kit.

MHW promised to clarify the approval procedure for the kit product by issuing an official notification. The contents will be as follows:

(1) The kit product itself will be treated as a drug in the approval process.

(2) When the manufacturer of a pharmaceutical, who has already obtained its approval, desires to manufacture a kit product using the already approved pharmaceutical, he is required to seek partial modification of the approval of the pharmaceutical (the processing period is within one year).

(3) When a manufacturer of a container and a solution (hereafter referred to as a "device manufacturer") desires to manufacture a kit, it shall apply for an approval for the kit and arrange for a partial modification of the drug approval, following simplified MHW procedures. It is understood that (a) the drug manufacturer is considered the formal applicant for the partial modification of the drug approval, and (b) the manufacturer applying for the kit approval must supply copies of the data (developed by either party) supporting the partial drug approval and the original shonin held by the drug manufacturer. Both approvals will occur at the same time and will be provided by MHW within one year.

The United States accepted the proposal with the following agreed clarifications:

(1) Approval requirements are essentially the same for device and drug manufacturers applying. For applications from device manufacturers, the two-part approval procedures will be handled simultaneously.

(2) Approvals will be granted in the same period of time irrespective of whether an application is filed by a drug or device manufacturer, initially no more than one year. MHW agrees to make efforts to shorten further the processing time and intends to do so when feasible.

(3) Either party, the device or drug manufacturer, may hold the manufacturing shonin and therefore can be the consignor.

(4) Commercial arrangements between the consignor and the consignee will not be interfered with by MHW. MHW will regulate the relationship only as regards the safety and efficacy of the kit product.

(5) Commissioned manufacturing is acceptable for all types of kits covered by MHW's proposal, which is intended to be a general solution for drug and delivery system combinations. The negotiations had focused on four kit types most commonly in use outside Japan and the proposal is based on these examples. The negotiators agreed to find in future follow-up talks practical resolution of any new problems that might emerge as kit technology advances.

b. Pricing

(1) The kit product itself will be treated as a drug in the reimbursement system.

(2) Considering the distinctive feature of the kit product, the reimbursement price will be set based on three cost elements: 1) the price in the drug tariff standard of the pharmaceutical contained in the kit; 2) the price in the drug tariff standard of the solution contained in the kit; and 3) the cost price of the non-pharmaceutical portion which shows the distinctive feature of the kit product. Pricing will be based on a formula which increases the sum of these three elements by a fixed percentage premium if the kit product demonstrates certain of the medical advantages from (1) to (4) which are listed in the first paragraph of this section. This premium, 3 percent as a standard, can range from a minimum of 1.5 percent to a maximum of 4.5 percent depending on the size of the sum.

(3) When the drug tariff standard is revised following the investigation of market prices of drugs, the general calculation rule for drug prices will be applied for the kit product based on the market price of the kit itself, regardless of the price of pharmaceuticals or solution in the kit.

c. Implementation

Official notices implementing the agreed approach for handling approval of kits will be issued in March 1986, to take effect on April 1, 1986. When kits have been approved according to such procedures, pricing will be executed in accordance with the aforementioned agreed approach.

F. CHANGE OF COUNTRY OF MANUFACTURE

1. Issue

Leading pharmaceutical and medical device firms of the world operate multinational manufacturing operations and frequently shift production locations from country to country in response to changing marketing and other business conditions. At the start of the MOSS talks, MHW's regulatory system required the procedure for modification of approval whenever a foreign firm wished to make such a change in manufacturing site for a previously approved product. The U.S. side stated that this procedure created an unnecessary cost of doing business in the Japanese market, and requested that MHW relax its approval modification requirements to permit foreign firms to change country of manufacture with simple notification to MHW.

2. Agreed Approach

For purposes of Japanese regulation of foreign medical device and pharmaceutical companies, a change in the country of production of already approved products will now require simple notification to MHW.

The relevant regulatory actions taken by Japan are as follows:

-- Ministerial Ordinance No. 26 (dated: June 29, 1985; effective: July 31, 1985).

-- Notification No. 658, "Implementation of the Ministerial Ordinance for Partial Revision of the Enforcement Regulations, Pharmaceutical Affairs Law" (dated: June 29, 1985; effective: July 31, 1985); No. 1 (2), "Items Related to Notification of Changes in the Source Country of Importing, etc., Approvals."

G. MINOR PRODUCT MODIFICATIONS

1. Issue

This problem concerned MHW's handling of minor product modifications (e.g., color changes or nonfunctional external design changes) that do not affect safety or performance of medical equipment, which did not require modifications of approval. MHW had no clear guidelines of which types of product changes required modifications of approval. The consequence, in the view of the U.S. side, was that foreign firms faced potential uncertainties and difficulties at import clearance, and that the introduction into Japan of products with minor modification could be impeded.

2. Agreed Approach

MHW has reconfirmed that minor changes in medical devices which do not affect safety and efficacy do not require modifications of approval. To clarify guidelines, MHW has made clear by official notice examples of minor product modifications that do not require modifications of approval. This information has been supplied to Customs authorities and related agencies.

The relevant regulatory action taken by Japan is as follows:

-- Notification No. 155, "Handling of Applications for Manufacturing or Import Approval of Medical Devices" (dated: June 29, 1985).

H. CHANGE OF ADDRESS OF IMPORTER

1. Issue

When an importer of an approved medical device or pharmaceutical product changes its address in Japan, for purposes of the confirmation that the structure and equipment of its facility are compatible with the legal standards as well as public accountability and maintenance of relevant approval records and adverse reaction data, MHW requires the importer to apply for a kyoka. The U.S. side stated that MHW procedures in this area required excessive documentation and often caused interruption of importers' business operations.

2. Agreed Approach

The United States and Japan agreed that (1) application procedures for a change of address by importers as well as manufacturers would be simplified by omitting documents that are irrelevant to the change of address (such as those related to items imported, qualification of technicians, or physician's certificate), and that (2) prior application for kyoka to change the address was acceptable in order to avoid interruption of business operations.

The relevant regulatory actions taken by Japan are as follows:

-- Ministerial Ordinance No. 26 (dated: June 29, 1985; effective: July 31, 1985).

-- Notification No. 658, "Implementation of the Ministerial Ordinance for Partial Revision of the Enforcement Regulations, Pharmaceutical Affairs Law" (dated: June 29, 1985; effective: July 31, 1985); No. 3, "Handling of Cases Where Factories or Business Offices are Moved."

I. SIMPLIFICATION OF IMPORT CLEARANCE PROCEDURES

1. Issue

At the outset of the negotiations, MHW required importers to obtain certificates for customs clearance through MHW officials which showed that the imported products (and the importers) complied with MHW regulations and conformed with applicable licenses (shonin, kyoka, et al.). The U.S. side said that these procedures caused costly delays and additional administrative work for importers. With this in mind, the United States and Japan discussed the simplification of import clearance procedures for approved products through a single clearance by customs, as is done in the United States.

2. Agreed Approach

It was agreed that:

-- Imports of pharmaceuticals and medical devices will now be permitted to pass through Japanese customs without MHW's individual certification (as was formerly required) when the importer presents a copy of the license (shonin and kyoka) or of the notification of clinical trials paper (as is required under the Pharmaceutical Affairs Law).

The relevant regulatory action taken by Japan is as follows:

-- Notification No. 667, "Request to Customs for Cooperation on Import Inspection of Pharmaceuticals, etc." (dated: June 29, 1985; effective: August 1, 1985).

J. HEALTH INSURANCE REIMBURSEMENT SYSTEM

1. Issue

The National Health Insurance system of Japan covers nearly 100 percent of the Japanese population. Therefore, reimbursement to physicians, hospitals, and clinics from the health insurance system is a dominant factor in the market entry of pharmaceuticals and medical devices.

The U.S. side stated that foreign manufacturers of drugs and devices have had great difficulty in understanding how MHW goes about setting reimbursement rates and that delays in setting reimbursement rates have caused unnecessary frustration and cost.

The MOSS discussion in this area covered three related issues: (1) the timing for setting reimbursement prices; (2) the criteria used in the official price-setting process; and (3) the transparency and public visibility of the process, including appropriate participation in the process by those whose products are ultimately priced.

The first issue concerned both the frequency of new pricing decisions and the related question of delays between manufacturing or import approvals and the establishment of reimbursement prices for approved products.

In discussing the second issue, the U.S. delegation sought information regarding criteria in evaluating products for pricing decisions and asked that these criteria be made public. The U.S. side was especially concerned about one criterion -- market penetration (i.e., general acceptance and use of a particular product by the Japanese medical community). This criterion, the U.S. side added, impeded market entry because it made pricing decisions difficult to obtain for innovative medical technology not uniformly available throughout Japan.

The Japanese side responded that it is proper for MHW to judge whether a particular medical technology should be available to the general public. The National Health Insurance scheme covers nearly 100 percent of the Japanese population and, therefore, MHW must be concerned with equity when judging how best to provide an adequate level of medical care for the people.

The Japanese side also explained that under a new program initiated in October 1984, medical devices that incorporate highly advanced technologies and that are intended for use at university hospitals and equivalent facilities will be reviewed after one year for reimbursement by an experts group of the Chuikyo. If MHW concludes after receiving this group's report that an item should be included in the National Health Insurance system, a reimbursement price will be listed in the next revision of the fees for medical services. The reimbursement system will

cover the ancillary costs involved in using the device during the period prior to the Chuikyo review. During the course of the MOSS talks in 1985, 16 highly advanced medical technologies in 56 cases at 31 hospitals received designation under this program.

Discussion on the third issue revolved around a similar request -- that not only decision criteria be made public but also that all interested parties be given opportunity to provide appropriate information and argumentation to responsible authorities (including the Chuikyo) in the price-setting process.

2. Agreed Approach

The United States and Japan agreed on the three issues in the health insurance reimbursement area as follows:

(1) The timing for setting reimbursement prices.

a. New drugs will be regularly listed four times a year in accordance with the timing of manufacturing or import approval for the purpose of their faster introduction into the drug tariff after their approvals.

They will be listed as soon as possible after their approvals, within 60 days in principle, and not later than 90 days.

This policy will be applied for new drugs approved in and after JFY 1986.

b. New medical devices and in-vitro diagnostics will be handled as follows, in accordance with the medical technologies for which they applied.

i. The highly advanced medical technology is initially introduced into the system of "highly advanced medical treatment" in which the basic charges such as hospitalization fees are reimbursed, after MHW consults with the expert group under the Chuikyo (the meeting is to be held once a month). MHW will introduce the product into the general reimbursement system at the time of the revision of the tariff for medical fees, if it recognizes the introduction as appropriate after one year from designation as a "highly advanced medical treatment."

ii. Other new medical technologies will be regularly introduced into the reimbursement system four times a year.

However, those for which new points should be provided under the "fee-for-service" reimbursement system will be introduced into the system at the time of revision of the tariff for medical fees. New innovative in-vitro diagnostics (Class I IVDs) will be introduced into the reimbursement system within six months after their approvals, with implementation by MHW in JFY 1986.

(2) The criteria used in the official price-setting process.

a. Opportunities for hearing from foreign as well as domestic industry representatives on general issues of reimbursement policy will be provided when the formula for the revision of the drug tariff standard or the calculation formula for prices of new drugs, each of which was established by the Chuikyo in September 1982, are changed. The formula will be made public.

b. The general rules for setting and revising prices of medical devices and in-vitro diagnostics will be established and announced by MHW, after consultation with the Chuikyo, in JFY 1986.

(3) The transparency of the process.

a. The opinions of foreign as well as domestic industry representatives will be heard in the Chuikyo, when the general rules of the tariff for medical fees or of the drug tariff are to be established or changed.

b. Opportunities to state opinions on their particular products will be provided by MHW for individual company representatives. The procedures for hearings will be made public and rules concerning the participation of the companies concerned will be made.

i. At the hearings, testimony on the efficacy, desired price, and other aspects regarding the product being applied for will be heard. The hearings will not be open to the public. If the originator so desires, he will be given the opportunity to attend with the applicant company and to state his opinions.

ii. The date and place for the hearings will be made public at least one week or 10 days before the hearings take place.

(4) The measures listed in (2) and (3) will be implemented in JFY 1986 after consultation with the Chuikyo.

K. TRANSPARENCY OF THE APPROVAL PROCESS

(Note: The issue of transparency in the price reimbursement decision process is covered in Section J on the health insurance reimbursement system.)

1. Issue

The United States and Japan affirmed the importance of transparency in health care regulation, as emphasized in the July 30, 1985, Action Program.

At the start of the MOSS talks, foreign firms felt that the operations of the CPAC and MHW in the approval process were not transparent enough and that the system made it unnecessarily difficult to solicit timely and relevant information from them and to transmit publicly information that would be of use to them. The United States and Japan discussed ways of increasing the transparency of the regulatory process in Japan for the benefit of Japanese and foreign manufacturers of pharmaceuticals and medical devices.

During the course of the talks, the U.S. delegation noted with appreciation that MHW had steadily increased both the frequency and the openness of formal and informal discussion on approvals and other matters with foreign firms and their representative groups. U.S. contacts with representatives of foreign firms revealed a high level of satisfaction on the part of those businesses with this progressive attitude of MHW officials at all levels.

2. Agreed Approach

With regard to the new drug approval process, it was agreed that:

-- The applicant will be given opportunities to hear instructions directly from the members of the CPAC, to ask questions, and to make comments on the Council's instructions.

-- The number of persons and the amount of time allotted to each applicant will be fixed beforehand.

-- The Council's "common instructions" will be made public and meetings will be held to explain them.

In addition, MHW will continue its successful policy of frequent, open, informal exchanges of information and discussion of regulatory matters with industry representatives, both individually and through organizations such as the American Chamber of Commerce in Japan (ACCJ) and the economic and commercial representatives of

the U.S. Embassy. As noted above, this progressive attitude has done much to promote harmony and good relations between industry representatives and MHW officials at all levels.

The relevant regulatory action taken by Japan is as follows:

-- Notification No. 664, "Transmission of Instructions Concerning New Drugs, etc., from the Central Pharmaceutical Affairs Council" (dated: June 29, 1985; effective: July 1, 1985).

L. BLOOD PRODUCTS AND OTHER BIOLOGICAL PRODUCTS

1. Issue

The U.S. delegation stated that Japan represents an important market for blood and other biological products and therefore its regulation of these products is important. In this view, the talks focused on two separate U.S. concerns:

-- The number and kinds of tests required of the manufacturer, the importer, and the Japanese National Institute of Health (JNIH) for release of these products, and the resultant delays caused by the redundant testing; and

-- The re-export of blood products and the degree to which foreign manufacturers can control their inventories for remanufacturing.

2. Agreed Approach

Experts from FDA and MHW met in Rockville, Maryland, in November 1985 to discuss the regulatory policies of both countries concerning the testing and release of blood products. As a result, the Japanese Government agreed to make the following changes:

-- To work toward the harmonization of international blood standards and eliminate obsolete tests. A positive step in this direction was taken when MHW published revised standards for blood products in October 1985.

-- To carry out inspections of foreign manufacturing facilities to determine compliance with good manufacturing practices (GMP) regulations. As for blood products which require national testing, MHW will accept test data from firms in compliance with Japanese GMP standards and will eliminate the need for the Japanese importer to repeat the tests before applying for national testing by the JNIH. For the present, in general, under the national testing program, potency, sterility, pyrogens, and abnormal toxicity will continue to be performed by the JNIH. (This measure will become effective April 1, 1986.)

On the second issue, the U.S. side recognized the Japanese policy which in principle prohibits the export of blood products. The Japanese Government does permit the re-exportation of blood products in the same form as they were imported and which do not violate their export policy, as in the case of blood products intended for remanufacture.

M. VITAMINS

1. Issue

The Japanese historically have used three criteria for regulating vitamins: (1) the shape or form of the product, (2) whether a dosage is specified, and (3) whether the manufacturer makes a health claim. According to MHW, if any of these criteria are likely to provide the average person with the understanding at the time of sale that the substance has a medicinal purpose, then it is classified as a drug. The criteria mentioned above are supported by the Japanese Supreme Court.

Within the MOSS discussions on this issue, the U.S. side first requested that MHW clarify its criteria for regulating vitamins. Upon receipt of the clarification, the U.S. side further requested that MHW eliminate shape and dosage requirements to permit the sale of vitamins as food supplements. Similar products that are sold as food supplements in the United States are being regulated as drugs in Japan. The U.S. side said that there are two difficulties in having a product regulated as a pharmaceutical as opposed to a food. First, a lengthy approval process exists for pharmaceutical products. Second, vitamins regulated as pharmaceuticals have a limited distribution system.

The Japanese side said that in their view, the regulation of vitamins must be decided on the basis of the historical background and national recognition of drugs in each country. Therefore, it is impossible to change the present Japanese criteria. In Europe, each country has its own system for regulating vitamins. The Japanese side said that the U.S. regulation is not the best because of problems of overuse.

MHW explained to the U.S. side its criteria used to regulate vitamins. MHW also explained that the procedure to get a premarket approval of vitamins as drugs is generally simple and that vitamins regulated even as drugs are widely available in pharmacies and drugstores without prescriptions in Japan.

In addition to the regulatory concern, the U.S.-Japan negotiating team tackled a related tariff issue. Vitamin preparations regulated as drugs are subject to a 4.9 percent tariff rate. Vitamin preparations regulated as foods, however, are classified as "miscellaneous edible preparations" and face a 25-28 percent tariff. The high tariff effectively makes foreign-produced vitamin preparations uncompetitive in the Japanese market. The U.S. side stated that the most appropriate resolution would be to eliminate the regulation of vitamins as pharmaceuticals, but resolution of the regulatory issue, without resolution of the related tariff issue, would create another problem for foreign manufacturers who previously imported products as drugs and paid only a 4.9 percent tariff, and then found themselves paying a 25-28 percent tariff to import their products as food.

2. Agreed Approach

a. FDA and MHW experts discussed regulatory issues in November 1985 in Rockville, Maryland. In these discussions, both sides recognized that significant differences exist in each country's national approach toward the regulation of vitamins. As a result, the United States and Japan have agreed to further meetings to explore and consider possible alternatives. Both sides also agreed that the promising solution to explore would be one involving regulation of vitamin preparations as over-the-counter drugs, with premarket approvals to be made as fast as possible. Among other advantages, this approach would remove the associated tariff problem, as such preparations would continue to be subject to the 4.9 percent tariff for drugs.

b. With regard to the tariff issue, at the end of the December talks the U.S. side presented a list of vitamin products which presently are regulated as foods. The Japanese side agreed to examine the matter as soon as possible based upon the materials provided by the United States.

c. The two sides had difficulty in agreeing on the time schedule for all of the issues, including that described in paragraph (b) above. The problem was that the issues had received their first intensive discussion at the experts' level in November 1985, and had not yet been discussed in any significant detail at the plenary, political level of the MOSS negotiation.

The two sides agreed to hold continued talks in the experts' group before the first follow-up meeting at the plenary level is held in 1986. The entire problem of vitamins will receive full vetting in the first plenary follow-up meeting at the political level in 1986, at which time schedules will be discussed and an effort will be made to resolve the problem.

N. STABILITY AND STERILITY TESTING

1. Issue

a. Accelerated Condition

In June 1984, MHW issued improved regulations for pharmaceutical products stored at room temperature which allowed the manufacturer to submit a new drug application accompanied by one-year interim stability data at room temperature and six-month accelerated stability data. For products which are not expected to be stable at room temperature, however (for example, products which require refrigeration), Japan had not defined acceptable accelerated test criteria. For such products, Japan required that the manufacturer wait until the full data of the long-term stability study under proposed conditions be available before submitting the new drug application. This meant that submission of the new drug application for such products had to be delayed until the real-time stability data had been generated.

b. Sterility Testing

Prior to the MOSS discussions, MHW regulations required that when an importer in Japan wanted to import an injectable product, the importer in Japan had to (1) have facilities to conduct sterility tests and animal tests, and (2) conduct them as acceptance tests. The regulation prohibited the foreign manufacturer or a third party in Japan from conducting these tests. The U.S. side said that when the importer did not have the facilities to conduct such tests, this requirement necessitated additional facilities investment which was both costly and time consuming.

c. Matrix Testing

The U.S. side raised the concern that in Japan real-time stability data had to be generated for all sizes and concentrations of drugs (including in-vitro diagnostics). In other words, the U.S. side believed that if a manufacturer produced a product with five concentrations and packaged it in five containers of different sizes, he had to generate real-time stability data for all concentrations at all sizes.

2. Agreed Approach

a. Accelerated Condition

Expert-level meetings took place at FDA in November 1985. As a result of those meetings, the Japanese side agreed that regardless of whether or not the product is stable at room temperature, a new drug application can be submitted if it is accompanied by one-year real-time stability data, accelerated stability test data, and severe test data, as defined in MHW's notifications (No. 406, March 31, 1980, and No. 718, May 30,

1980). The method for conducting the accelerated study on the products which are not expected to be stable at room temperature can be decided by the manufacturer and will be evaluated by MHW on a case-by-case basis.

The applicant will be required to continue the real-time stability test to completion after the new drug application is submitted. All real-time data must be submitted to MHW and will be reflected in the approval.

This measure will be effective April 1, 1986.

b. Sterility Testing

Both sides agreed that sterility tests (and animal tests) for pharmaceuticals and medical devices can be contracted out to certain Japanese labs certified to conduct such tests. The importer, however, remains responsible for quality control of the products. This measure will be effective April 1, 1986.

c. Matrix Testing

As the result of the experts meetings, the Japanese side clarified for the United States that as of June 8, 1984, long-term stability tests are not required for all different concentrations and volumes of a drug. Long-term stability, severe, and accelerated tests are only required for one product considered to be most sensitive under the storage conditions, and only simple accelerated tests or relative comparison tests are required for all other concentrations and volumes as shown in the example below. The MHW procedures will permit some flexibility in applying these stability testing standards when reasonable grounds exist.

	Volume		
	10ml	20ml	50ml
Concentration			
5%	(a)(b)(c)	(d)	(d)
10%	(c)	(d)	(d)
20%	(c)	(d)	(d)

(a) Long-term stability test (b) Severe test

(c) Accelerated test (d) Relative comparison test

III. TECHNICAL EXPERTS GROUP

During the course of the MOSS talks, both sides agreed that several factual questions raised during the discusions required the attention of technical experts. Consequently, a technical experts' group was established to discuss these detailed matters under the instructions of the Japanese and U.S. delegation leaders. These discussions proved fruitful and actually led to the resolution of certain issues through close scientific consultation at the technical level, without requiring negotiation at the plenary level. As a result, the two sides agreed to continue the experts' group's existence as a forum for similar discussions in the future. The group will meet on an *ad hoc* basis as issues arise.

IV. FOLLOW-UP

As shown in the detailed descriptions in Chapter II of the issues discussed in these MOSS talks and the agreed approaches to solutions, the subject matter of the discussions was highly complex. Agreed solutions could not in all cases be easily reduced to simple, comprehensive statements.

The thrust and intention of both sides in the talks, however, was to produce agreements that would simplify administrative procedures, eliminate administrative delays, increase transparency, further facilitate access to Japan's market for medical equipment and pharmaceuticals, and thus strengthen the free trade system with special reference to this industry sector. Given these shared objectives, both sides recognized that further discussions will be required, as implementation continues, to discuss any complications that arise and to handle related issues that need to be raised and resolved. Indeed, several of the "agreed approaches" detailed in Chapter II make special reference to the negotiators' commitments to find practical solutions to real business problems, and to the anticipation that further discussions in a follow-up process may well be needed to obtain such solutions.

To facilitate this need for ongoing discussions, therefore, both sides agreed to schedule regular follow-up meetings, approximately every six months during 1986 and on schedules to be decided in later years as necessary, at sites to be decided. These follow-up discussions will be at the plenary level. The meetings will review the implementation of the agreed solutions; review foreign firms' experience with the new rules and procedures that have been agreed upon; and resolve any related issues that may arise as experience accumulates.

V. GLOSSARY

Japanese Terms

Chuikyo	-	The Social Insurance Medical Affairs Council. Advisory body to MHW which deliberates the total amount of reimbursement and the general rules for reimbursement prices. The Chuikyo is made up of representatives of payers and payees of insurance reimbursement, and of the public interest.
CPAC	-	Central Pharmaceutical Affairs Council. Advisory body to MHW which investigates from a scientific point of view whether it is appropriate to approve manufacturing or import of new pharmaceuticals or medical devices.
JFY	-	Japanese fiscal year.
MHW	-	Ministry of Health and Welfare.
NHI	-	National Health Insurance system.
PAL	-	Pharmaceutical Affairs Law.
quasi-drugs	-	Products with mild effects on the human body, such as mouth washes, baby powders, etc.
reimbursement price	-	Prices given to pharmaceuticals, medical technologies, etc., by MHW for reimbursement under the National Health Insurance system.

U.S. Terms

FDA	-	Food and Drug Administration.
time clock	-	Period during which health regulatory officials evaluate medical products to determine safety and efficacy.

General Terms

biological products	-	Products derived from biological sources, such as plasma, vaccines, etc.
clinical tests	-	Tests performed on people to determine the safety and efficacy of a product.
GMP	-	Good manufacturing practices.
IVDs	-	In-vitro diagnostic reagents. Products used in outside-the-body tests, such as rabbit serum used for urine pregnancy tests.
"me-too" drugs	-	Generic drugs.
OTC drugs	-	Over-the-counter drugs.
pre-clinical	-	All tests conducted prior to clinical testing, including animal tests.
procedure kit	-	Combination of medicines with their delivery systems in single package.
stability tests	-	Tests that measure how time, temperature, and other conditions affect the quality (potency, etc.) of drug compounds.
stability tests, accelerated	-	Tests that simulate the conditions of real-time stability tests in an accelerated period, producing comparable results. An accelerated stability test may replicate in six months what a real-time stability test would do in two years or more.
stability tests, real-time	-	Stability conducted under the actual conditions (time, etc.) for which data are being sought to determine the shelf-life of a product.

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